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Exposure to Dose Models: Their Uses in Helping Access Relevant Dose in Children

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This talk will switch gears just a little bit and that you'll see at least for the first part of it some emphasis on exposure, and what are exposure to dose models. And, of course, basically what we're after

What are Exposure to Dose Models?

- Mathematical descriptions of toxicologically relevant internal doses
  - Doses result from actual or realistically simulated exposures
- Dose estimating portion of model is centered around physiologically based pharmacokinetic (PBPK) models

Here, based on the discussion of the last couple of days , I defining a toxicologically relevant dose. In our research we think we're on the right track to helping out. That is, we're looking at exposure to dose models. These are mathematical descriptions of toxicologically-relevant doses, and these doses we think need to result from realistically-simulated exposures or from actual exposure measurements and exposure conditions I'm part of an exposure research laboratory so you'll hear an emphasis on the importance of some exposure elements in things, which we haven't talked about too much in the last couple of days here. The part of the exposure-to-dose model that estimates dose is centered around a physiologically-based pharmacokinetic model, or I should say physiologically-based pharmacokinetic models, and we've heard a little discussion about that the first day and a half, and then this afternoon we've heard a lot more discussion. I think the three talks this afternoon, Dr. Hattis', mine and the next one, sort of come into play here because there's a great deal of variance and, in fact, something Dr. Hattis said will come back here in this presentation, that is that the variability in certain physiologic and biochemical parameters may be greater in children, and that's of concern to us as we'll show here.

Toxicologically Relevant Doses

- Depend upon mode of action
- Different possible measures depending upon the health effects of concern
- Examples
  - Parent compound
  - Metabolite
  - Parent or metabolite bound to endogenous molecules

Now what we mean by toxicologically relevant doses is illustrated in the next slide I often tell my students when they ask a question I can't answer, I say, "Well, it depends." And that's the rule here too, it depends upon the mode of action, and we heard yesterday a good definition of mode of action and mechanism of action, so probably this slide should say depends on the mechanism and modes of action. Also there are different possible measures depending upon the health effects of concern, and this can be true for one exposure chemical; there can be several different measures or metrics of dose that we want to use that are relevant depending upon the health impact. One of the chemicals that I'm using here as an example, perhaps not the best example for this symposium, but one of the chemicals I'm using here is trichloroethylene (TCE). And again, if we're looking at a nervous system narcosis, for example, it is one species, likely the parent compound. If we're looking at some of the long-term health effects (e.g., cancer) it's some of the metabolites. So again, it depends upon the mode of action and it depends upon the health effect of concern.

I've listed here a couple of things such as the parent compound, the metabolites, or the parent or metabolite bound to endogenous molecules. And I think with the discussion of the first day and a half of this workshop or symposium, that happens to be probably a measure of dose that will be used more and more frequently as the biologists give us more information on that mechanism of action.

Now the measures of the relevant dose also depend upon a number of things

Measures of Toxicologically Relevant Doses

- Depend upon mode of action, endpoint of interest, monitoring strategies, and why models are being used
- Examples
  - Peak concentration
  - Steady-state concentration
  - Amount metabolized
  - Area under the concentration or amount curve
  - Rate of metabolite formation

Again, they depend upon the mode of action, they depend upon the end point of interest, and they depend upon monitoring strategies and why the models are being used in the first place. Again, remember I come from an exposure laboratory, and frequently the exposure scientists come to me and ask me how should we monitor, in field studies, so that we give the most relevant and useful information back to the toxicologists and risk assessors. And our role on the dose area is to be the intermediary between those two disparate groups and try to give them some useful information. It may be that the item of interest for the toxicologist or the clinician, or the risk assessor, is the peak concentration, or it may be that they're interested in some type of steady-state concentration which is somewhat analogous to the discussion that Dr. Portier had this morning about body burden; sometimes steady-state concentrations match very well with body burden. It could be the total amount metabolized. I think you heard Dr. Portier quote some of Dr. Dedrick's earlier work about the total amount of a compound over a lifetime. Well, another analogous measure to that is the total amount metabolized over a certain specified time, sometimes the whole lifetime.

The area under the concentration vs. time curve, or the area under the amount curve that Dr. Hattis described, is a frequently used measure by risk assessors as an estimate of dose. It is used in the dose response curve. A new one that I think we've heard some interesting information on in the last day and a half is the rate of formation of a metabolite or the toxicologic species of interest.

There have been some speculations that, for example, in a few cases of acetaminophen poisoning that occurred, irrespective of the fact that there may have been some co-exposures with ethanol, that what may have happened there was the rate at which the acetaminophen was delivered to the liver created an overwhelming burden for the liver of the toxic metabolite that was formed. Now, that's a simplistic explanation of the acetaminophen toxicity, which isn't really clear. But the point is that the amount of formation and the rate at which the formation occurs can be an important measure of dose, and sometimes describes the toxic results mathematically better than some of those other measures that I've listed in the slide.

Now pharmacokinetic models or physiologically based pharmacokinetic models are nothing more than mathematical descriptions of the time course of the disposition of the chemical and the biotransformation products within the body

PBPK Models

- Mathematical description of the time-course disposition of chemicals and their biotransformation products within the body
- Describe the actual physiologic, anatomic, and biochemical processes within the body

They are based around, and they describe actual physiologic and anatomic and biochemical processes within the body, as best we think we know them and as best we can measure them. For example we'll use organ volumes, blood flows, permeation ients, and binding constants based on experimental data. Now I think in the panel discussion a little earlier there was some discussion, and Dr. Portier mentioned that a good pharmacokinetic study on any one of these compounds could cost upwards of a quarter of a million dollars, and that's the downside of this. Because these models are based on a number of these physiologic and anatomic processes they're expensive to do. On the other hand, cross-benefit analysis, they may end up being cheaper than having tons of animal bioassays that weren't conducted properly or weren't conducted to give us the right information.

You can't read this slide very well , but essentially what happens is the biologist comes in and asks the mathematician "could you please describe this in layman's terms," and the mathematician says "what, this is in layman's terms."

There are a couple of rules about pharmacokinetic modeling, it's not rocket science after all, I've been doing it for 15 years or 20 years. On the other hand, for every physiologist that comes in and thinks that he can describe what's going on in an organ or a body, basically mass balance, there are at least ten engineers out there who can write the equations. And for every engineer who can write the equations there are at least ten mathematicians who can take those equations and put them into a completely unintelligible form. And that's kind of where we are here, why it often looks more difficult than it really is.

Some of the examples of the PBPK model parameters are shown here

Parameter Examples

- Anatomic
  - Body and organ volume
  - Body and organ composition
- Physiologic
  - Blood flows
  - Absorption rates
  - Clearance
  - Breathing rates
- Biochemical
  - Metabolic rates
  - Binding constants

As I mentioned, there are the anatomic parameters, the physiologic parameters and the biochemical parameters. Now, some points of interest here are that we do know a lot about the anatomic parameters and the physiologic parameters and how they differ among individuals and how they differ amongst age groups. There's a fair amount of information out there, or so we thought. Actually, when I began looking into the literature about the variance in some of these parameters what I found was that although there was a lot of information, the information was about a very specific population. It was about adults, about white males predominantly. [And the database is accurate through about 1975 or 1980] There are some more databases out there now but they're hard to find and they're not complete. So even with adults we have, in fact, quite a few data gaps. With children it's even more of a problem. A number of the ways that you figure out what the anatomic parameters should be, even the averages, forgetting the distributions, is by doing body weight extrapolations or body weight to some power which takes you to 3/4 of surface area (2/3) power extrapolations. And in reality that has not been substantiated across the age groups, because those extrapolations are also based on information that has been derived from, and for, adults. So even with the well-characterized anatomic parameters, the well-characterized physiologic parameters, some of which were measured hundreds of years ago, even with that we don't have a good handle on how to vary those amongst children.

But where the real problem comes, as I think Dr. Hattis mentioned earlier, and Dr. Ginsberg in the next talk will mention even more, are in the biochemical parameters, like binding constants and metabolic rate constants. We just don't know a whole lot about how they vary from chemical to chemical, of course. But we don't know a lot about how they vary from individual to individual, particularly across age groups. And I think some of the work that Dr. Hattis showed in working with the pharmaceutical information is our best chance at getting some of that kind of information out. It's just not going to be possible to do it other ways, or at least not in direct measurements in children. There are some possibilities of some other techniques and structure activity comparisons and so on. One of the things that we always ask ourselves in our exposure laboratory, are children's exposures anything special? There are a number of things that can make children's exposures special . In this slide we see a case where we have activities of concern. And when I use activities for the rest of this talk there's going to be some confusion because of the way I did the slides. I can divide activities up, in terms of exposure, into two categories.

Exposure Considerations

- Concentration
- Contact route
- Duration and location
- Frequency
- Personal activities

One is where the activity impacts the exposure concentration in the environment. So for example, if we have a substance in water, in tap water that can volatilize, activities such as dish washing, turning on the faucet, boiling water for coffee, flushing the toilet, for example, those activities can impact the exposure concentration. But then there are activities, personal activities that impact the actual exposure of the individual. The child crawling around playing with toys, crawling around in the crevices, for example, does that make him or her special for terms of exposure and so on. And that's when we talk about activities, so we're talking about also a dual track for activities, if you will

Concentration

- Children spend much time in special locations
  - Schools
  - Day care centers
  - Buses
  - Home playrooms, bedrooms

So some of the considerations that fall into that, of course, are the exposure concentration. How much of the chemical's there, how much of it goes from one medium to another. In pesticide spraying, for example, how much of it stays in the carpets, how much of it stays in the walls, and then how much of it finds its way to other vectors such as the dust. As the activities make that dust circulate throughout the environment, that affects an exposure concentration. So measuring what's on the carpet, for example, may not be an accurate reflection of the exposure concentration because the child may be getting it into the body by inhaling the material that's semi-volatile on the dust.

The contact route

Contact Rate Issues and Special Activities

- Hand-to-mouth behavior
- High incidence of certain foods and beverages
- Food as a vector from the floor, pets, and other locations of contaminants

Are children special because of their contact route? Toddlers in particular? We know they crawl around on the floor, we know they have lots of activities. So is there something special about that contact route? Do they have more special considerations because they spend more time on the floor, and so on and so forth? Are there things that are different about the children's skin that make adhesion or, in fact, permeation different in children versus adults?

The duration and the location, it's quite clear that that plays a role. I'll talk about the impact of duration of exposure a little later on pharmacokinetics. And, in fact, duration in a sense is really reflective of activity, how long does a child spend in contact with a particular foreign chemical that we have concern about, how often. And then, of course, the personal activities.

Some of the special considerations are that children spend a lot of time in special locations: schools, day-care centers which have not been well characterized as of yet, buses, and home. Special areas in the home such as playrooms, bedrooms, sometimes even in worked-over garages or the basement playrooms. They spend a great deal more time than the rest of us do in these very special locations and so there may be special considerations there in terms of exposure.

The contact rate in special activities. Children, as we all know, do a great deal of hand-to-mouth behavior. But in addition to hand-to-mouth behavior, that sometimes goes hand to food to floor, back to food, to pet, to mouth behavior.

You know, the great thing is to give a kid a hot dog. A hot dog is a great thing because , it's got a built-in handle, and if you watch a toddler with a hot dog a lot of times they'll take a bite out of it, then they'll roll it on the floor because it's just great for rolling on the floor. While we're at it let's go put it in the corner and see what kind of gook we can put on it, and now we'll stick it a little bit in the dog's mouth. Then we'll stick it in the dog's ear -- I better stop with that analogy. (Laughter.) And then the child takes a look at the hot dog and says, "Oh, gosh, let's take another bite." And so now we've had a tremendous transfer of things.

And pediatricians tell me about that and then I refer that to our exposure people and they look at me like you're crazy if you think we can go into a home and do this. We actually had an adult trying to act like a toddler in one of our studies. And let me tell you, we had a very, very tired person at the end of about three hours.

Exposure studies have shown that children have a high incidence of exposure to certain foods and beverages. At different ages that vary, there's a high incidence of fruit juices and things of that nature and so that's of concern, again, particularly when we're concerned about pesticide residues in those foods. And I mentioned about food as a vector. My favorite story about the hot dog and the dog.

The models that we're developing, the concept is that they can simulate or reproduce actual exposure conditions.

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Contact Rate Issues and Special Activities

- Hand-to-mouth behavior
- High incidence of certain foods and beverages
- Food as a vector from the floor, pets, and other locations of contaminants

And we take into account the routes of exposure, the different media, the frequency, the duration, and the time history of concentration, if available. So we can input these conditions into the models. I think Dr. Portier mentioned this morning the rapid change in computational capabilities. I think they will be our great ally here. For those who are mathematically inclined in the audience, when you take a look at some of these time history concentrations, or even the simulated exposure there when you try to simulate exposures that change very rapidly with respect to the rest of the system, that's a computational challenge to do it in a time where the model runs faster than our lifetime. So I think with the new computational developments we'll be able to do a great deal more.

We try to make these models, as I mentioned earlier, to be an accurate representation of the body and, of course, they need to consider the variance and uncertainty. This is particularly important I think in all age groups, but certainly important in an age group such as [newborns and very young infants?] that I suspect, and I agree with Dr. Hattis, have a greater variance.

EPA has developed the dose-estimating exposure model,

EPA's Dose Estimating Exposure Model (DEEM)

- Core
  - PBPK model
- Exposure Input Modules
  - Multiple routes
  - Multiple chemicals
  - Multiple exposure scenarios
  - Sensitivity and variance modules

the core of which is the pharmacokinetic model as I mentioned earlier. We can do all of these things with multiple exposure scenarios, sensitivity of the various models and so on. I'll move on with that since I've already mentioned it. The PK part of the model can be configured to have any of several body organs as compartments. So for example, at any one time you could come and say, "well, gee, we're interested in what's going on in the brain", so we can reconfigure the model relatively easily and then given the right physiological and thermodynamic parameters, we can try to estimate the relevant dose in the brain. Or I suppose we could even take in the thymus if we could figure out what the anatomic parameters for it are before it disappears.

So far we have used the well stirred flow limited assumptions of a model, which isn't, by the way, always a great assumption, but nonetheless that's what we have used at this point with a couple of exceptions. When we go into certain organ compartments in the skin we go into permeation-driven modules.

PBPK Core of the Model

- Can be configured with any of several body organs as compatments
- Generally – well stirred, flow limited
- Several circulating chemicals and metabolites
- Equilibrium binding
- Enzyme induction and inhibition

The model as we have it configured can also handle simultaneous exposure to multiple chemicals, can have circulating metabolites from any of these chemicals so that we can begin to test the interaction, at least simulated interaction between different chemicals. This morning I heard a talk about the role of ethanol with exposure to some other compounds and those are the kinds of things that, given the right information from the animal studies, or the human studies preferably, we can simulate. Now we have binding in there and also the ability of enzyme induction or enzyme inhibition as well. With the exposure modules we can take a look at the typical routes of exposure, inhalation, ingestion, dermal. We have the injection routes particularly because the model can also be used by the toxicologists to reproduce or simulate the animal experiments.

Exposure Modules

- Several routes
  - Inhalation
  - Ingestion
  - Dermal
  - Injection routes
- Exposure events
  - 9 separate events possible for each route
  - Time history of exposure concentration

The concept is that we can have nine separate repeating exposure events for each route. We could, for example, simulate a toddler being exposed on a regular basis to something in the diet and at the same time on an intermittent basis to something in a beverage and something intermittent by following the dog around the house or something of that nature. Again we're an exposure laboratory so we have exposure people who like to go out and measure exposure concentrations at least on the personal space and they like to do that with time. We have exposure modelers who use mechanistic-based models and then do probabilistic simulations of what a time history of exposure is, and we then input that into our model so that we can calculate relevant dose based on that exposure history. Well, this says it's not perfect, and it clearly is not, but it's better than the wheel we had. Our feeling is that this is much better because I think the toxicologists, at least based on what I've seen for the last day and a half, need to know more about what's going on at the molecular level as opposed to some concentration outside and say, “yeah, we just ate four pounds of something in the last two days.” Well, what does that really mean inside the body?

What are the issues that are likely to matter here? Well, we need to select the proper dose metric. Rapidly changing measures of dose are affected, as our work is starting to show, usually by variable exposure profiles.

What Then is Likely to Matter?

- Need to select the proper dose metric
  - Rapidly changing measures of dose are usually affected by exposure profiles
  - Longer, integrated measures are less affected by changes in exposure profiles

So I tell the exposure folks if that's what the toxicologist is interested in you're going to have to go out and spend lots of money and measure exposure very carefully with a good time resolution. The longer, more integrated measures are less affected by changes in exposure profiles, but may be more affected by physiologic and biochemical differences amongst individuals and within an individual. So now I turn around and tell the biologists and biochemists you have to spend the money to go and figure that kind of stuff out. Because really these models are not any good if we don't have the proper input data and the proper information to put it in.

If you want to believe in your model and it's any good, one of the things you do is you look for real live data to compare it to and see if the model is doing a reasonable job. In fact, if the model predicts it too well you pretty much assume your model's wrong because you got lucky because it shouldn't, because we really don't understand what goes on completely in the body. But then one of the things I like to do when I'm doing a presentation is to take the data off so that it makes it easier for you to see the model output. What I've done for the next few slides is a number of different things. Again, we were working on two or three different projects having to do with trichloroethylene, and we had a couple of questions that the toxicologists wanted us to answer and a couple that we thought of ourselves to answer, and could we use the model to do this.

Well, the first thing we did was we developed the trichloroethylene model based on others that were published and some information that we got from the literature. Second, we compared it with some data in human volunteers that were graciously supplied to us by Dr. Jeff Fisher. And we took a look at that data and made sure that our model was a reasonable prediction, and we used several end points. Dr. Fisher's data was unique in the pharmacokinetic world because it not only gave us air concentrations, it gave us exhaled air concentrations of the parent compound, it gave us blood concentrations of the parent compound, it gave us blood concentrations of several metabolites, and it gave us urine concentration of several metabolites. Now that's a pharmacokineticist's dream. The reality is we usually do not see those kinds of data. So the reason we picked trichloroethylene and not something more interesting to this group like chlorpyrifos is because those data don't exist at that kind of resolution. So, therefore, you end up having a model that you think might be right. Here at least we have compared it with some data and we've done some other things using that data to further develop the model, which I won't get into here.

What these slides are intended to show is some of the results that we were looking for to answer one question

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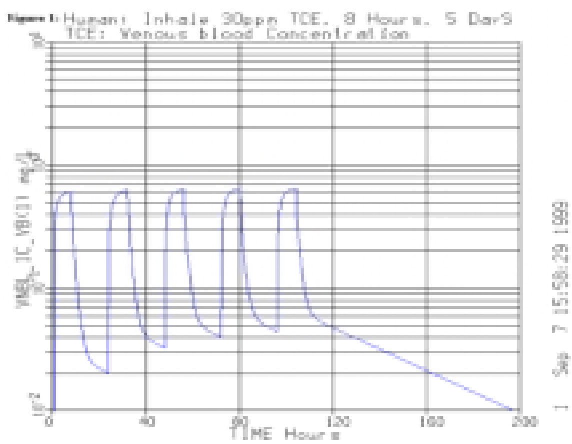

Can we measure over the course of several days but do sort of a time-weighted average over eight or nine hours, or do we have to measure in more minute-to-minute resolution. And the answer of course, as I've already given away, depends on the end point that you want.

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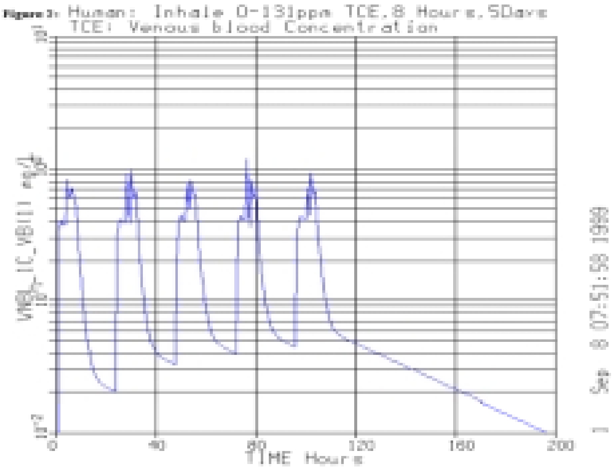


So what we did was two simulations. One where we simulated the exposure to be an eight-hour average, and the other where we took that same time-weighted eight-hour average and did all kinds of random exposures, simulating different occupational exposures if you will, one where perhaps the worker is exposed continuously for eight hours at a low level, and the other where the worker is exposed at bursts, sometimes high, sometimes low, sometimes even at zero level.

Dr. Portier referred to this dose rate issue this morning in his talk, and this is looking at it from the modeling perspective. And what we found is that if you're looking at the parent (TCE) concentration here, which happened to be trichloroethylene in the blood, this would apply even if it were a metabolite that were very rapidly formed and very rapidly eliminated. It turns out that the exposure profile is very important if you want to know about the peak concentration or the area under the curve of the concentration above a certain level (compare SLIDE 19 profile with SLIDE 18). Then it becomes very important.

Thus, for the parent compound which has rapid disposition

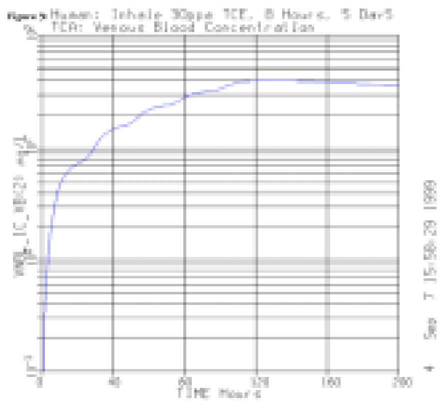
- The rapidly changing exposure scenario simulated here showed the highest peak blood concentration that was two-fold higher than any peak in the average exposure scenario
- The time of the peaks were considerably different
- The AUC above a certain level may be different

So the rapidly changing exposure scenario that's simulated here showed a very high peak blood concentration, first of all, that was twofold higher. Now I could have picked a different random pattern that wouldn't have shown that. The point I'm trying to make here is that the pattern was very important in establishing what the peak was. Now I have a couple of friends who are anesthesiologists and when I asked them what's important, let me tell you, for them the peak concentration is very important, because if they go above that peak they have a major lawsuit on their hands.

So as a result there are cases, even in the toxicology area, if narcosis is the issue for example, when the peak concentration is very important. By the way, in the occupational scenario that is important sometimes with volatile chemicals such as TCE.

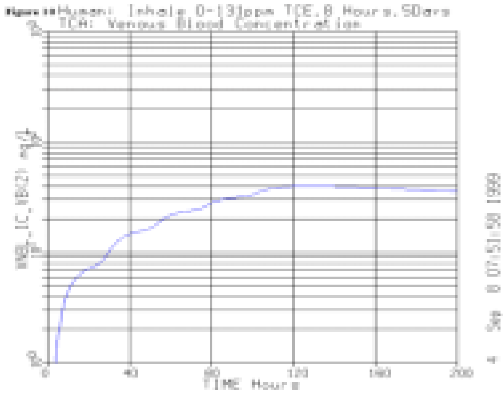
The time to the peaks were considerably different, and that can be important from a toxicological end point, we've seen some indication of that. And again, the area under the curve above a certain level might be different. So if it's some area under the curve above a threshold that you're interested in, one exposure scenario may never get to that threshold, the other one may. And so this sort of illustrates the importance of the exposure scenario

For the metabolite with the 8-hour average exposure



Next what we looked at was a key metabolite of TCE, the metabolite was quickly formed but very slowly eliminated, it was held in the body a long period of time. Again, it doesn't have to be the metabolite, it could be the parent compound, I just happened to choose the metabolite here . What we found was that the plateau level, in other words where it reached, not a true steady state, but a leveling off, was identical with the two exposure scenarios, it really didn't make any difference.

For the metabolite when the exposure is rapidly changing



The height of the plateau was about the same for both exposure scenarios. So the average concentration and the duration of the exposure are sufficient measures for the exposure person to go out and collect longer-term exposure data. If the exposure person gives me an eight-hour time-weighted average, what I need to know is, what the average concentration is and how long the exposure is, and how frequent if we want to repeat this over the course of days or weeks.

But the minute-to-minute changes aren't that important for this metabolite. Now that can save the exposure measurement people a lot of time, a lot of effort, a lot of money, and it can give us a lot more meaningful data because they can do so much more that way.

For this case

- The plateau level and the time to reach the plateau are identical
- For this endpoint the average concentration and duration are sufficient information for dose estimation; minute to minute changes in exposure concentration have little impact
- This “integrating” nature of concentration occurs when metabolites are readily formed and slowly eliminated

And probably a lot of this is because of the integrating nature of the body. Now unfortunately, a lot of the relevant measures of dose that I think Dr. Portier talked about this morning, and Dr. Hattis talked about, and that I mentioned earlier, are somewhere in between these apparent extremes.But the point is that with this type of modeling approach we can start to hint at the answer so this helps us a great deal not only in working a data analysis but in working on experimental designs.

Some of the other things we that looked at are summarized in the next slide (SLIDE 24): the concentration of the parent compound in the blood, the area under the blood concentration times the time curve for the parent TCE, and for the long-lived metabolite. These are some of the metrics that are most important for this chemical.

Now again remember at the very beginning I made a caveat that what I meant by activity, that I broke the word "activity" up into two pieces. One was the personal activity that dealt with the children running around the carpet and how it impacted what was in their individual exposure range versus the activity in the home that created an exposure concentration, turning on the water, turning on the dishwasher etc. The activity that I mentioned on this slide , and this is a little bit confusing, I should have clarified this, has to do with turning on the water, turning on the shower and so on.

Importance of Other Things Looked At:

- Concentration of Parent in Blood:
  - Exposure Concentration>Activity>Physiologic Variance
- Area Under the Curve of Parent:
  - Exposure Duration>Exposure Concentration>Physiologic Variance>Activity
- Area Under the Curve of Long-lived metabolite:
  - Duration>Physiologic Variance~Concentration~Activity

The activities that are personal activities for the child, let's say, or the worker, or the person in the home really are reflected more in things like exposure concentration and in duration, and in frequency particularly. What I'm getting at here is that this very simple case, it's not meant to be generalized, for something that was very rapidly changing in the blood, clearly the exposure concentration and the activity was very important. In this case the activity of how often the water was turned on, when it was turned on, all of those details, minute-to-minute details of the exposure were very, very important.

When we did an analysis on the physiologic variance, while that was important it was actually less important than what was going on, on the exposure side at that point. When we were looking at things like area under the curve for the parent that sort of fell in between, and then area under the curve for the long-lived compound, in this case it was a metabolite, clearly there were two things that overwhelmed everything else. One was the duration of exposure and the other, even though my slide doesn't indicate that, was the physiologic variance.

Now I'll tell you why the physiologic variance had a little less importance here. I figured it out this afternoon, or Dr. Hattis explained it to me. The duration is really an activity situation. How long was the child, in this case it was an adult, but how long would the child be exposed to something, how often did they go play in the corner and rub the hot dog around, and then how many bites of the hot dog did he take? That's clearly key information that we need to describe whether children are at greater or lesser risk.

In this case the physiologic variance probably had a lesser role because I think we simulated the physiologic variance for adults. I think based on what Dr. Hattis said earlier, the physiologic variance for children will be greater, and thus more significant, than that for adults.

We've done some other work where we have looked in the literature trying to find base levels of some of the different enzymes that we know convert toxic chemicals and work on toxic chemicals. What we find for that first year of life just substantiates what Dr. Hattis has found with more rigor.

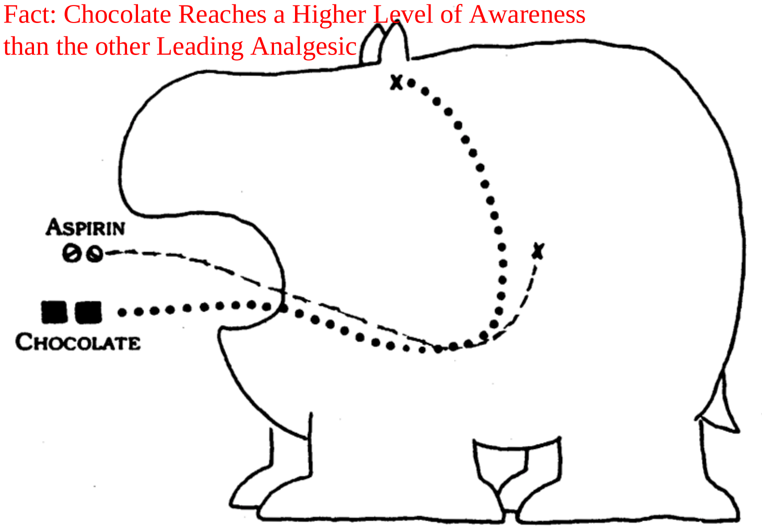
What we find in that first year is that not only are there variances quantitatively, but there are shifts in the enzyme systems that are used. There are enzyme systems that the neonate uses that suddenly stop, the enzyme system doesn't disappear, but in a sense that enzyme system is no longer used after about a year. So there's actually a shift qualitatively in the pathways that are used.

And that kind of variance is not reflected here; this was an early study we've just done, finished using the model. And again, it was for a different purpose, it was really to look at adults. So I think the impact of the physiologic variance is going to be far greater than what we've found so far.

So what have we learned ? Well, essentially clearly what we've learned is that the chocolate reaches a higher level of awareness or consciousness than the other leading analgesic, and that's perfectly clear from my talk today.

Well…

Fact: Chocolate Reaches a Higher Level of Awareness
than the other Leading Analgesic



And it really comes back to the other point of what I said at the beginning, that how you look at things depends, and what's happening here is that the lady goes up on the scale and the scale gives her, these old penny scales that used to exist, now I guess they're quarters, gives her little advice for the day, and it says the more mass an object has the greater its force of attraction, and then it says "you are extremely attractive."

And so, it all depends on how you look at things!

So it really depends on how you look at things. (Laughter.)

And I think I'll close at that point. (Applause.)

DR. BROWN: Are there any questions for Jerry?

DR. GINSBERG: In the exposure scenario that we're very interested in, it seems from pressure-treated wood, copper arsenic, the pesticide used in CCA wood that leaches out of the wood and forms a residue right on the surface, and then a child wiping a handrail or sitting on the deck can easily get a coating, there's been some studies showing a coating on the hand of arsenic. And we really don't quite know how to parameterize the amount of arsenic from that dust coating on the hand that actually gets into the mouth. So it's a hand-to-mouth kind of activity but how much of that dust goes down?

DR. BLANCATO: Rather than answer the question let me put a plug in for some other work that's going on at the exposure laboratory that's done by Dr. Ozkaynak and Dr. Zartarian of EPA.

They have a model at's, Mike, help me with this, it's called SHEDS. It's a probabilistic model that takes a look at issues like that where they have the activity simulated where the child crawls around and touches surfaces, and then with the hand-to-mouth, well, first it does a what we call dermal loading. The next step will be to develop that model for the hand-to-mouth transfer. Now there are two limitations with that. First, it's been for pesticides, and second, it's been the transfer to the dermal so it needs to be expanded a little further. In fact, the model will be published in Environmental Health Perspectives, I can't remember the date but I think it's within the next two months.

DR. BROWN: Are there other questions for Jerry?

I'd like to ask a question. You mentioned the increasing computational speed of our computers, I know that some of the PBPK models that ran overnight several years ago now run in a couple of minutes. Are we heading for some sort of an equivalent to a gene chip in pharmacokinetic modeling where we can look at not only mixtures of chemicals but-I keep thinking of that slide that Elaine Faustman showed with the variations in the P450 enzymes at different phases of development, coupling that even with interindividual differences -are we heading for being able to tackle something like that with our computers in the next few years?

DR. BLANCATO: Well, the way computers are changing -- I mean, and if you're in charge of purchasing any you know that 20 minutes after you get it out of the box it's outdated. I mean, my wife always says to me, "Gee, you've got a brand-new computer," I say, "Yeah, but it's old already."

And so I guess the answer to that question is probably yes, and I think Chris Portier was alluding to that this morning. But I have to tell you that even what I showed you here -- well, not so much what I showed you here, but the business with the physiologic variance, actually with the exposure, when we looked at the exposure activities we did over 250 repeated simulations, if you will, of a random exposure pattern over a 24-hour period. And when we run that on a typical desk top P.C., one of the newest ones, I mean, we're not talking about minutes here, we're talking about a few hours worth of simulation time, so it's still a relatively slow procedure, but five years ago I wouldn't have been able to do that simulation.

DR. BROWN: Any other questions?

Okay, thank you, Jerry.

DR. BLANCATO: Thanks. (Applause.)